Anoxia and the Convulsive State

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SUMMARY

The author believes he has clinical and experimental evidence to suggest that one of the underlying causes of idiopathic epilepsy lies in lack of sufficient oxygenation of the cerebrum before or during birth.

REVIEW of the records of patients referred to the author because of convulsions disclosed that in a considerable number of cases there was history of abnormality in the mother during pregnancy or of difficulty with delivery. Accounts of bleeding, placenta praevia and profound narcosis for delivery were rather frequent. Curiosity as to whether such episodes might be just as frequent in instances in which convulsions had not appeared in the child led to the study here reported.

The literature revealed that others already had given thought to the question of relationship between difficulty in birth and convulsions in the child—one investigator some 80 years previously. Little, in 1862, had this to say:

"The object of this communication is to show that the act of birth does occasionally imprint upon the nervous and muscular systems of the nascent infantile organism very serious and peculiar evils. When we investigate the evils in question, and their causative influences, we find that the same laws of pathology apply to diseases incidental to the act of birth as to those which originate before and after birth."

The surprising thing is that Little stated that he believed that the mechanism at work was not direct trauma to the infant as it traveled through the birth canal but that it involved the "interchange of blood" between mother and fetus. He went on to state that he had observed that in cases in which the infant lived following premature birth, difficult labor, or mechanical injuries to head and neck during parturition, convulsions followed the act of birth and were liable to be succeeded by a determinate affection of the limbs of the child. And this, of course, is the basis for Little's Disease.

It is surprising that between 1862 and the last decade the possibility of "faulty interchange" was explored very little and apparently little thought was given to the question. During this time there were many papers on birth injuries as conventionally thought of—that is, in terms of damage to the cranium, petechial hemorrhages in the central nervous system, subdural hemorrhage, or laceration of the surface veins or of the intracranial venous sinuses—but there was not much on the possible effects of anoxia. Instead, there was a good deal of work on methods of resuscitation of asphyxiated infants.

It was not until the last decade that a publication by Schreiber of Detroit served to reawaken interest in the clinical aspects of anoxia suffered during fetal life and at birth. He reported on almost 500 cases of infants and children who showed neurological defects, and found that in the majority there was history of difficult birth. Less than a year later Cole and his co-workers in Detroit published the results of a study based on 5,000 deliveries and aimed at investigation of asphyxia of the newborn. These investigators appear to have established the following:

1. *Prematurity* is the greatest factor in asphyxia.
2. *Trauma* is an important factor.
3. *Narcosis* and *general anesthesia*—in whatever amount used—definitely are prejudicial to the infant's respiration.

It appears from this study that the safest birth from the point of view of asphyxia of the newborn is that in which no sedative, analgesic or anesthetic is used.

Irving, Berman and Nelson, studying apnea of the newborn, found that apnea was least when no anesthetic was used. They progressed through a list of drugs and combinations of drugs until they got to a combination of Pantopon [R] and scopolamine. When this combination was employed, 67 per cent of infants were apneic at birth.

Faber was chiefly interested in cerebral atrophy, although in his series of cases half the patients had convulsions. He applied Barcroft's outline of anoxia to the conditions causing anoxia in the fetus and newborn infant. He reiterated four points that applied to anoxia and damage to the nervous system, from whatever source the anoxia might proceed: (1) The earliest and most disastrous effect of oxygen deprivation is exerted on the central nervous system, particularly the cerebral cortex and basal ganglia. (2) Complete anoxia causes death of the affected nerve cells in three to ten minutes. [The author believes the cells may die in even shorter periods of anoxia.] (3) The lower centers being less susceptible, the infant may survive months or years with irreparable damage to the cortex. (4) The effect of repeated exposures to anoxia is cumulative. [The author does not believe this has been proven as regards humans.]

Clifford, in 1940, showed that in placenta praevia with pronounced hemorrhage the infant mortality rate is very high. Moreover, the infants who died after several days showed changes in the brain compatible with the state produced by anoxia.

Although it does not apply directly, mention should be made of the important work of Courville,

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who several years ago published a monograph on the subject of nitrous oxide anesthesia. His neurological material included a number of cases in which the infants died, had paralyses of various sorts, or immediate or delayed convulsions. The important thing to remember is that nitrous oxide, administered by an inexperienced person, may be a very dangerous agent. Its deleterious effects, however, are due solely to anoxia—not to any especial property of the gas. In this respect it operates as do other simple asphyxiants such as helium, nitrogen, methane, and carbon monoxide. In the past ten years a number of investigators have made studies based on the researches of Haldane, Barcroft, Henderson, Peters and van Slyke. Barcroft's classification of anoxia has become widely accepted.

Some of those who in the past decade have studied the effects of anoxia experimentally are Yant and his co-workers, Himwich, Windle and Becker, and Kabat and Yaskin. Largely out of their work the following generalizations have been drawn:

The central nervous system demands a lot of oxygen. The cerebrum has a more active metabolism than any other organ in the body and the rate of irrigation of the brain is tremendous. At the same time, neurological tissue is more sensitive to oxygen lack than any other tissue in the body. Further, there is an unfortunate gradient: The gray matter of the cerebrum and cerebellum demands, as Yaskin pointed out, the most oxygen; the white matter of the cerebrum and cerebellum demands less; and the spinal cord least of all. This agrees with the tabulations Drinker made of survival time under conditions of anoxia of various portions of the central nervous system. Drinker noted that, when deprived of oxygen, tissues of the central nervous system survived as follows: cerebrum, small pyramidal cells, 8 minutes; cerebellum, Purkinje's cells, 13 minutes; medullary centers, 20 to 30 minutes; spinal cord, 45 to 60 minutes; sympathetic ganglia, 60 minutes; myenteric plexus, 180 minutes. There is rather rough confirmation of this gradation in the very careful work of Yant and others who carried out studies on pathologic changes produced by anoxia in dogs. Various changes such as chromatolysis, distortion of nuclei, vascular stasis, vacuolization and fragmentation of the cells and perineural edema tended to be most pronounced at the highest level — the cortex, thalamus and corpus striatum. In the brain stem and cord, and at lower levels, the changes tended to be less extensive.

At the most sensitive level, serious effects may follow oxygen deprivation for as short a period as 90 seconds; death of the cell may occur in anywhere from three minutes upward. In this connection, as has been pointed out elsewhere, the period of seconds or of minutes during which the obstetrician sees the newborn child as exhibiting good color, crying lustily, breathing at once, does not furnish a basis for a decision that the child is normal. It must be recalled that interruptions of the supply of oxygen, even for a short period, at any time during the entire period of gestation, may produce lasting damage that may not be apparent at once.

So much for the important clinical and laboratory studies of the last ten years. It will be noted that none of the investigators studied the correlation between anoxia and the later development of convulsions.

Beginning such a study, the author scanned his own records of patients suffering from the convulsive state. The history in every one of these cases was taken by the author. It might also be mentioned that the patients come from the lower middle class and are a pretty uniform group.

All cases in which the history of pregnancy and birth was inadequate were discarded. In many such instances nothing was known or recalled about the birth history. Also discarded were those cases in which there was some other possible explanation for the convulsive state—such as cerebral cyst, tumor, meningitis, or encephalitis. Remaining for study were 37 patients, up to 25 years of age, who would be labeled in most quarters as persons with idiopathic epilepsy.

Of the 37 patients, 12 had histories of what appeared to be normal pregnancy and delivery. In two cases there was history of mild abnormality in pregnancy or birth that may or may not have been significant, but the patients were included in the 12 with normal history in order to avoid weighting the figures in support of the thesis of this presentation. In 25 of the 37 cases, or about 66 per cent, there was what was considered a significant abnormality of pregnancy or delivery. These included: Placenta praevia, 2; significant bleeding during pregnancy, 6; significant false labor, 6; prolonged labor (48 hours or more) with evidence of asphyxia at birth, 9; toxemia of pregnancy, 2.

The question that arose was, "Are these birth histories really unusual?" To answer this, the birth records of a small control series of children in the 10 to 15 age group who never had had a convulsion were examined. These were records of patients who had been ill enough to come to the clinic or into the hospital because of some other complaint such as upper respiratory infection, rheumatic fever, a broken bone, or appendicitis. Interviews with the parents were carried out at Stanford, at the San Francisco Hospital and at the Children's Hospital. A standard questionnaire was used. Forty such cases were investigated. In only four, or 10 per cent, was there any suggestion of abnormal birth history.

Comparison showed, then, that 66 per cent of persons who would be called idiopathic epileptics were found to have abnormalities in birth histories, whereas only 10 per cent of those who had never had a convulsion were found to have unsavory birth histories. The author consulted a statistician who felt that this was a significant disparity.

In laboratory experiments pregnant bitches, whenever possible within the last week of pregnancy, were subjected for periods of 20 to 30 minutes to an atmosphere in which the oxygen content was

lowered to as little as 4 per cent (Fender, Neff, Binger). Carbon dioxide was not allowed to accumulate and in all samples ran less than 1 per cent. The equilibrium of the atmosphere was controlled by the washing through of nitrogen and oxygen. The enclosure was of glass so the animal could be observed. A separate port allowed frequent sampling of the gas within the tank so that determinations could be made.

Experimental procedure: The animal was placed in the tank and nitrogen was turned on. The "clinical" condition of the animal determined what was done next, an attempt being made to keep it barely alive during the 20-30 minutes. At the end of this period the animal was returned to room air. After a short period that often included defecation, urination, inability to stand, then ataxia in walking, the animal returned to normal state if it survived.

One bitch aborted the evening of the experiment and ate her young. Twenty-three other pups born 24 to 72 hours after the experiment (most of them within the first 48 hours) died within the first few weeks following. Three survived permanently without apparent neurological involvement. Two pups, one of them in a litter of two and the other in a litter of three, developed status epilepticus at five and six weeks respectively. The first was killed after 24 hours to end its state, and the second survived for three days, having almost constant seizures. Motion pictures were made of these convulsions.

To summarize: Of the 23 pups that could be counted, 18 died rather promptly; of the five survivors, three seemed to be normal and two had convulsions.

DISCUSSION

As a generalization it may be said that something (or several things) produces a change that is either structural, chemical, or electrochemical, in the cortex or other high level of the cerebrum. This change makes it possible for something periodically to be built up or to disappear, which in turn reaches an electrochemical trigger level that fires off a convulsion.

The author proposes that anoxia is one of the agents that may produce this primary change, and that it may be one of the major causes of so-called epilepsy.

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Discussion by J. M. NIELSEN, M.D., *Los Angeles*

Dr. Fender is to be congratulated on the facts and theories he has adduced. Dr. Courville and I have been interested in this subject for about 18 years. Statistical data on asphyxia are difficult to gather, because the patient cannot know, the mother rarely knows and the obstetrician seldom can remember the circumstances at birth in a given case. Therefore, since it is known that there is greater incidence of difficulty with the birth of a first child than with subsequent births, I took a new avenue of approach—a study to determine whether epilepsy is more common in the first-born than in other offspring of the same mother. It has been possible to gather excellent records of nearly one thousand suitable cases. I will not bother you with the details, but it turned out that the rate of incidence of epilepsy was twice as great in the first-born as it was among any subsequent children of the same mother. It seems to me that if we can give more attention to this factor we may be able to prevent much epilepsy.